REMARKS

Applicant respectfully requests reconsideration. Claims 1-9 and 13-19 were previously pending in this application. Claims 10-12 were withdrawn by the Examiner. Claims 2, 7-9 and 13-19 have been canceled without prejudice or disclaimer of the right to pursue such claims in a continuing application.

Claims 1, 3 and 6 have been amended to clarify the claim language..

New claims 20 and 21 have been added. New claim 20 specifies a method according to claim 1 which comprises screening for expression of mRNA transcripts of the E6 gene of at least one additional HPV type which is known to be prevalent in the geographical area or population under test. Basis for this claim is to be found on page 21, lines 27-28. New claim 21 specifies a method according to claim 1 which additionally comprises screening for expression of mRNA transcripts of the E6 gene of HPV type 52 and/or HPV type 58. Basis is to be found on page 21, lines 16-24.

As a result, claims 1, 3-6, 20 and 21 are pending for examination with claim 1 being an independent claim. No new matter has been added.

Sequence Compliance

The Examiner required the Applicant to provide a Sequence Listing including the sequences found on pages of the specification. Applicant has amended the specification to insert sequence identifiers in the text and also has filed herewith a Sequence Listing. Applicant accordingly respectfully requests reconsideration.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1-9 and 13-19 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) The Examiner rejected the claims as indefinite based on the use of the term "high-risk". Applicant respectfully disagrees that this term renders the claims indefinite. As is clearly stated in claim 1, the claimed methods include sorting the subject into one of two categories of risk for development of cervical carcinoma based on expression of E6 mRNA. Individuals positive for expression of E6 mRNA are classified as high risk for development of cervical carcinoma, whereas individuals negative for expression of E6 mRNA are classified as no detectable risk for development of cervical carcinoma. Therefore Applicant contends that the claims are distinct and not indefinite

(b) The Examiner suggested that the term "wherein" be substituted for the term "characterised in that" in claims 1 and 2. Applicant has deleted this term from claim 1 and has canceled claim 2.

(c) The Examiner indicated that the term "abnormal cell changes in the cervix" renders claim 2 indefinite. Applicant has canceled this claim, rendering this rejection moot.

(d) The Examiner requested that acronyms NASBA, ASCUS and CIN1 in the claims be spelled out. Applicant has done so.

(e) The Examiner indicated that the term "preferably" renders claims 8 and 18 indefinite. Applicant has canceled these claims, rendering this rejection moot.

Accordingly, withdrawal of the rejection of claims 1-9 and 13-19 under 35 U.S.C. §112 is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1-9 and 13-19 as failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicant respectfully requests reconsideration.

Applicant has amended claims 1 and 2 to recite that the subject is screened for expression of mRNA transcripts of the E6 gene of HPV types 16, 18, 31, 33 and/or 45.

Applicant therefore respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1-9 and 13-19 under 35 U.S.C. § 103(a) as being unpatentable over Lorincz (WO 99/29890 A2) in view of Leone et al. (Nucleic Acids Res. 1998 May 1;26(9):2150-5; "Leone"). Applicant respectfully traverses the rejection.

With regard to the teachings of Lorincz, a key difference between the method of the invention and the method of Lorincz is that the method of the invention classifies patients as "high risk" or "no detectable risk" for development of cervical carcinoma based purely on a yes/no determination for expression of E6 mRNA transcripts from the claimed selection of HPV types. In contrast, the method of Lorincz classifies patients on the basis of a calculated ratio between the levels of expression of mRNA transcripts of the E6 and/or E7 genes and the levels of expression of mRNA transcripts from the E2 and/or L1 genes. The method of Lorincz thus

requires accurate quantitation of expression level of at least two genes, and the calculation of a numeric ratio between the expression levels in order to assess the stage of HPV-based disease (see summary of the invention on page 4, lines 20-24 and claims 1-5). The method of the invention thus differs from the method of Lorincz in that it requires detection of expression of E6 transcripts alone, not a combination of two or more transcripts.

The Examiner has acknowledged on page 12 of the Office Action that "Lorincz does not expressly teach categorizing people based on expression results". However, the Examiner considers that Lorincz must "clearly suggest" such a method step. In fact, Lorincz does expressly teach that individuals can be classified according to the stage of HPV-based disease, but Lorincz teaches that this classification should be based on relative expression levels of two or more HPV transcripts.

Example 2, to which the Examiner refers on page 12 of the Office Action as allegedly teaching a method comprising screening for expression of E6 transcripts, is in fact carried out on CaSki cells, which is a cell line containing approximately 600 copies of an integrated HPV type 16 genome. Example 2 merely exemplifies *methodology* for measuring E6/E7 mRNA *for use* in the disclosed method, and shows that the methodology works to detect E6 transcripts in the CaSki cell line, which contains a very high copy number of HPV type 16. There is no teaching or suggestion in Lorincz of a method in which *human test subjects* are classified as "high risk" or "no detectable risk" as recited in the claimed invention purely on the basis of a yes/no determination of E6 mRNA expression alone. This difference is an unobvious distinction between the Lorincz method and the method of the invention. Lorincz teaches that it is necessary to determine a ratio of two different transcripts in order to determine disease status in a patient. Moreover, Applicant notes that Lorincz does not contain any actual data from patient samples to substantiate that the method works in practice.

The method of the invention also differs from the method of Lorincz in that it requires only a simple yes/no determination of "E6 expression" or "no E6 expression" in order to classify patients as "high risk" or "no detectable risk". Thus, there is no need for accurate quantitation of

E6 expression levels, or calculation of numeric ratios, in order to practice the method of the invention.

Both of these factors considerably simplify the methodology required to practice the method of the invention in comparison to the method of Lorincz, yet the method of the invention has been shown by extensive clinical studies to achieve high specificity for identification of individuals at "high risk" of developing cervical carcinoma.

Furthermore, Lorincz does not disclose the specific combination of HPV types listed in the current claim 1, and also fails to teach that expression of E6 mRNA alone can be used to classify individuals as "high risk" or "no detectable risk" for developing cervical carcinoma in respect of each and all of the claimed HPV types.

To summarize, Lorincz clearly teaches that it is necessary to quantitate expression levels of at least two transcripts, one of which is from a gene other than E6, and determine a numeric ratio of expression levels, in order to classify the stage of HPV-based disease in a human subject. There is no suggestion in Lorincz that subjects can be classified as "high risk" or "no detectable risk" for developing cervical carcinoma based on E6 expression alone.

With regard to the teachings of Leone, the Examiner asserts that Leone teaches real-time monitoring of NASBA reactions using molecular beacons and one-tube amplification and detection. Leone does not teach or suggest any of the elements missing from Lorincz as set forth above, nor does the Examiner suggest that Leone teaches or suggests these elements.

Therefore, the combination of the Lorincz and Leone references does not provide all of the elements of the claimed invention. The combination does not teach or suggest that expression of E6 mRNA alone can be used to classify individuals as "high risk" or "no detectable risk" for developing cervical carcinoma in respect of each and all of the claimed HPV types

Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Lorincz in view of Leone is respectfully requested.

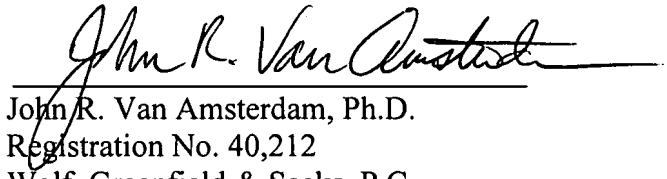
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: July 24, 2007

Respectfully submitted,

By: 

John R. Van Amsterdam, Ph.D.
Registration No. 40,212
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000

WGS Date: x07/25/07x